FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

VIA SIGNATURE CONFIRMED DELIVERY

January 10, 2019

David W. Hill, Owner
Belmar Select Outsourcing, LLC
12860 W. Cedar Drive, Suite 211
Lakewood, CO 80228-1971

Dear Mr. Hill:

You registered with the U.S. Food and Drug Administration (FDA) as an outsourcing facility under section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) [21 U.S.C. § 353b][1] on November 9, 2017. From August 25, 2016, to September 2, 2016, FDA investigators inspected your facility, BSO LLC, located at 12860 W. Cedar Drive, Suite 211, Lakewood, CO 80228-1971.

During the inspection, the investigators noted deficiencies in your practices for producing sterile drug products, which put patients at risk. FDA issued a Form FDA 483 to your facility on September 2, 2016. FDA acknowledges receipt of your facility's response, dated September 21, 2016, and your updated responses, dated November 10, 2016, and March 9, 2017.

Based on this inspection, it appears your facility is producing drugs that violate the FDCA.

A. Compounded Drugs under the FDCA

Under section 503B(b), a compounder can register as an outsourcing facility with FDA. Drug products compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility qualify for exemptions from the drug approval requirements in section 505 of the FDCA [21 U.S.C. § 355(a)], the requirement in section 502(f)(1) of the FDCA [21 U.S.C. § 352(f)(1)] that labeling bear adequate directions for use, and the Drug Supply Chain Security Act requirements in section 582 of the FDCA [21 U.S.C. § 360eee-1] if the conditions in section 503B of the FDCA are met.[2]

[1] *See* Pub. L. No. 113-54, § 102(a), 127 Stat. 587, 587-588 (2013).
[2] We remind you that there are conditions, other than those discussed in this letter that must be satisfied to qualify for the exemptions in section 503B of the FDCA.

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An outsourcing facility, which is defined in section 503B(d)(4) of the FDCA [21 U.S.C. § 353b(d)(4)], is a facility at one geographic location or address that — (i) is engaged in the compounding of sterile drugs; (ii) has elected to register as an outsourcing facility; and (iii) complies with all of the requirements of this section. Outsourcing facilities must comply with other provisions of the FDCA, including section 501(a)(2)(B) [21 U.S.C. § 351(a)(2)(B)], regarding current good manufacturing practice (CGMP), and section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)], regarding insanitary conditions. Generally, CGMP requirements for the preparation of drug products are established in Title 21 of the Code of Federal Regulations (CFR) parts 210 and 211.

B. Violations of the FDCA

Adulterated Drug Products

The FDA investigators noted CGMP violations at your facility that caused your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the FDCA. The violations include, for example:

1. Your firm failed to clean, maintain, and, as appropriate for the nature of the drug, sanitize and/or sterilize equipment and utensils at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements (21 CFR 211.67(a)).

2. Your firm failed to establish time limits for the completion of each phase of production to assure the quality of the drug product (21 CFR 211.111).

3. Your firm failed to establish adequate written procedures for production and process control designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess (21 CFR 211.100(a)).

Outsourcing facilities must comply with CGMP requirements under section 501(a)(2)(B) of the FDCA. FDA's regulations regarding CGMP requirements for the preparation of drug products have been established in 21 CFR parts 210 and 211. FDA intends to promulgate more specific CGMP regulations for outsourcing facilities. FDA has issued a draft guidance, *Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act*. This draft guidance, when finalized, will describe FDA's expectations regarding outsourcing facilities and the CGMP requirements in 21 CFR parts 210 and 211 until more specific CGMP regulations for outsourcing facilities are promulgated.

C. Corrective Actions

In your responses dated September 21, 2016, November 10, 2016, and March 9, 2017, you described certain corrective actions. While several of your proposed corrective actions appear adequate, we still have the following concerns.

1. In your response to the inadequate cleaning issue, your firm provided Utensil, Glassware and Bottle Cleaning Validation (PQ004.1.VP & CV004.1.VR) and Residual Cleaning Validation (CV005.1.VP). Your firm stated in CV004.1.VR that testosterone and estradiol were used in these validation studies because "both drugs are compounded (b) (4) in the BSO cleanroom, whereas Anastrozole and Progesterone are punched (b) (4) " You also stated that "it has been noted that Estradiol has (b) (4) " and concluded that "Estradiol would be potentially, the most difficult to clean." However, you did not provide any data to support Estradiol is the most difficult-to-clean product. CV004.1.VR also stated that "the bottles have been determined the hardest item to clean based on access into the bottle due to neck size of the bottle." However, you did not provide any data to support this statement and it is not clear how you evaluated equipment such as the (b) (4) which appear to be difficult to clean. The Residual Cleaning Validation (CV005.1.VP) does not appear to include (b) (4) tooling and (b) (4) tooling of the pellet press equipment, while your Press Qualification (EQ002.1.VR) states that "tooling used on the presses are (b) (4) " Therefore, it is unclear if the cleaning of tooling has been validated. Furthermore, in both validations mentioned above, it is unclear how you established the acceptance criteria of (b) (4) for residual drug substances and it appears that your firm did not establish recovery rates for these products.

2. In response to the hold time observation, you provided reports of Hold Time for Pellets Prior to (b) (4) (PV006.1.VR) and Hold Time for (b) (4) Results (PV007.1.VR). In PV006.1.VR, the bioburden was determined by (b) (4) (b) (4) However, it is unclear if the drug pellet was (b) (4) and bioburden from the entire pellet was adequately recovered during the process. In addition, this validation study states that "Testosterone and Estradiol both require (b) (4) and both of these drugs are compounded (b) (4) in the BSO cleanrooms, where as Anastrozole and Progesterone are punched (b) (4) and the API does not require (b) (4) process. Based on the (b) (4) (b) (4) of use at BSO and that the process of punching pellets through (b) (4) is the (b) (4) , Estradiol and Testosterone pellets will be used for pellet hold time study." However, you did not provide data to demonstrate Testosterone and Estradiol represent the worst case as compared to Anastrozole and Progesterone.

   Regarding the Hold Time for (b) (4) Results (PV007.1.VR), we have the following concerns. This report used an acceptance criterion of no more than (b) (4) for each sample, which appears to be significantly higher than (b) (4) the bioburden level indicated in the 2015 Sterile Pellets Sterilization Validation Report (PQ002.01.VR). You stated that (b) (4) of (b) (4) were pulled at each time point for testing, but you did not provide details on where the samples were pulled. In addition, your studies yielded a potency result of 110.10%, which is out of the specification of (b) (4) Your firm did not provide any explanation or investigation on this result.

3. In response to the process control observation, you provided process validation reports for the punching equipment used in your facility (b) (4) (b) (4) EQ002.1.VR, EQ003.1.VR, and EQ004.1.VR). You stated in these reports that

"since all four drugs manufactured at BSO, Testosterone, Estradiol, Progesterone and Anastrozole are (b) (4) Testosterone will be used during equipment qualification. Testosterone pellets are punched (b) (4) whereas Estradiol is punched (b) (4) (b) (4) and Anastrozole or Progesterone are punched either (b) (4) (b) (4) This justification for using Testosterone during your operational qualification, based on the (b) (4) instead of the characteristics of the drug substance and difficulty to produce, is inadequate. You listed lubricants used in the pellet punching process in Attachment 1 of your response dated March 9, 2017, and stated that some of the lubricants are food grade. However, it is unclear if all product-contact lubricants are suitable for implantation. In addition, thickness, as a dimension parameter, was not included as a specification in the validation studies.

In addition, the operational qualification (OQ) did not encompass the full range of operation. For example,

a. Your products range from 6 mg to 200 mg with multiple weights in between. However, you only validated Testosterone at two weights, 25 mg and 200 mg.
b. You appear to use several sizes of dies. However, you chose only one size die for your validation studies.
c. The pressures for the blunt pellets range from (b) (4) with various values in between. However, you chose only (b) (4) in your validation for the blunt end pellets.
d. The validation for (b) (4) did not state the quality of the compressed air or if the load cells were calibrated.

In the report of Process Validation for Estradiol/Testosterone (b) (4) (PV009.1.VR), it is unclear if one or multiple locations were sampled. Limited sampling locations may bias the results. In addition, acceptance criteria did not include particle mean and distribution of the (b) (4) or loss of moisture during the (b) (4) process. A (b) (4) was performed to determine the bioburden in the (b) (4) of both products. However, this process decreases the limit of detection to below the acceptance criterion of (b) (4)

Additionally, should your firm compound and distribute drug products that do not meet the conditions of section 503B, including the condition that drug products be compounded by or under the direct supervision of a licensed pharmacist, the compounding and distribution of your drugs would be subject to the new drug approval requirement, the requirement to label drug products with adequate directions for use, and the Drug Supply Chain Security Act requirements.

D. Conclusion

The violations cited in this letter are not intended to be an all-inclusive statement of violations at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all requirements of federal law, including FDA regulations.

Within thirty working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations. Please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you do not believe that the products discussed above are in violation of the FDCA, include your reasoning and any supporting information for our consideration. If the corrective actions cannot be completed within thirty working days, state the reason for the delay and the time frame within which the corrections will be completed.

Your written notification should be addressed to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food & Drug Administration
19701 Fairchild
Irvine, California 92612

If you have questions regarding any issues in this letter, please contact CAPT Matthew R. Dionne, Compliance Officer via email at Matthew.Dionne@fda.hhs.gov or by phone at (303) 236-3064. Please reference unique identifier 544261 in any submitted response.

Sincerely,

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

SP:mrd